



## King's Research Portal

DOI:

[10.1016/j.psyneuen.2018.12.233](https://doi.org/10.1016/j.psyneuen.2018.12.233)

*Document Version*

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Innes, S., Pariante, C. M., & Borsini, A. (2019). Microglial-driven changes in synaptic plasticity: a possible role in major depressive disorder. *Psychoneuroendocrinology*, 102, 236-247.  
<https://doi.org/10.1016/j.psyneuen.2018.12.233>

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

**Microglial-driven changes in synaptic plasticity: a possible role in  
major depressive disorder**

Stuart Innes<sup>a</sup>; Carmine M. Pariante<sup>b</sup>; Alessandra Borsini<sup>b\*</sup>

<sup>a</sup> Guy's King's and St Thomas' School of Life Science and Medicine, King's College London, UK - double check this is correct as has been updated

<sup>b</sup> Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

Postal Address: The Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology & Neuroscience, King's College London, Cutcombe Road, SE5 9RT, London, UK.

\* Corresponding author; [alessandra.borsini@kcl.ac.uk](mailto:alessandra.borsini@kcl.ac.uk)

Word Count: 6006 Including abstract not figure legends

References: 114

## **Abstract**

Recent data gathered from both *in vitro* and *in vivo* models of Major Depressive Disorder (MDD) have indicated that microglia play an active role in modifying some of the most important sources for neuronal plasticity, specifically long-term potentiation (LTP) and long-term depression (LTD). In addition, microglia have been implicated in neuro-immune interaction dysregulations, which are considered a core constituent of MDD pathology. While prior studies have investigated the diverse effects activated microglia can have in the context of depression, including regulation of inflammatory cytokine production and structural changes, recent evidence has revealed a more direct relationship between microglial activation and changes in synaptic function and plasticity, including LTP and LTD. Here we review these findings from animal models, as well as discuss how current preclinical evidence might shed light on novel therapeutic targets for patients with depressive disorder.

## Synaptic plasticity: long-term potentiation and depression

Microglia have been implicated in many neuropsychiatric conditions as potential mediators of change to neuronal function and drive pathology in major depressive disorder (MDD), bipolar affective disorder and schizophrenia (Mondelli et al., 2017; Notter and Meyer, 2017; Yirmiya et al., 2015). Although several mechanisms have been proposed to explain microglia driven impairment in neuronal function (Yirmiya et al., 2015), a growing body of evidence has recently shown that changes in synaptic plasticity, specifically in long-term potentiation and depression (LTP/LTD) might be microglia dependent, and therefore potentially relevant in the context of depression (Liu et al., 2015b; Milior et al., 2016; Riazi et al., 2015; Zhang et al., 2014a). Indeed, LTP and LTD play an important role in sculpting neural circuits to store new information in the hippocampus, a region highly involved in cognition, learning and plasticity, as well as in antidepressant response (Dale et al., 2016; MacQueen et al., 2008).

In the healthy brain, synaptic plasticity occurs constantly with the refining of inter-neuronal communications resulting in many vital brain functions (Bliss and Collingridge, 2013; Lynch, 2004). Whilst synaptic plasticity can express in many forms, the two most closely studied, with regard to learning and memory are LTP and LTD. Whilst simplistically LTP and LTD either facilitate or inhibit synaptic transmission, there is a considerable amount of heterogeneity in both forms of plasticity, which are considered to be umbrella terms for many different forms of synaptic modification. Briefly, LTP and LTD can be elicited by activation of N-methyl-d-aspartate (NMDA)-type glutamate receptors, typically by the coincident activity of pre- and postsynaptic neurons. In particular, the early phases of expression are mediated by a redistribution of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors, where more receptors are added to potentiate the synapse, or receptors are removed to weaken synapses (Herring and Nicoll, 2016; Lüscher and Malenka, 2012).

Whereas, with time, new proteins are synthesised, including protein kinases and phosphatases and this phenomenon will coincide with the occurrence of proper structural changes (Collingridge et al., 2010).

### **Altered synaptic plasticity in MDD**

As both LTP and LTD are believed to represent cellular correlates of learning and memory (Herring and Nicoll, 2016; Lüscher and Malenka, 2012), these two forms of plasticity have attracted considerable interest especially for their role in distinct psychopathologies, like depression, which are characterised by cognitive impairments. Indeed, evidence coming from animal models of MDD have reported altered synaptic plasticity following exposure to stressful stimuli, supporting the notion that plasticity may be critical for establishing and reversing a depressive behavioural state (Liu et al., 2015b; Milior et al., 2016).

Changes to synaptic plasticity in MDD have also been identified in human studies using repetitive transcranial magnetic stimulation (rTMS), which has been shown to alter cortical excitability in a similar manner to stimulation protocols for inducing LTP and LTD (Cantone et al., 2017). In particular, studies of cortical excitability and by extension neuronal plasticity in MDD, have reported consistent evidence for changes in LTP-like plasticity in patients with depression. Using a paired associative stimulation protocol, with transcranial stimulations, one study has identified impaired LTP-like plasticity in MDD patients who possess reduced motor evoked potential amplitudes, when compared with healthy controls (Kuhn et al., 2016). This finding was particularly interesting, as these reductions in motor evoked potential amplitudes were restored after MDD patients had entered remission (Kuhn et al., 2016). Therefore, overall evidence coming from both animal and human studies seems to suggest a possible involvement of synaptic plasticity in the cognitive deficits often reported in patients with depression.

## **The role of microglia**

Although a potential association between brain plasticity and MDD has been suggested, the exact mechanisms underlying any changes in synaptic function in the context of depression still have to be elucidated. Since glial cells, astrocytes and microglia tightly and dynamically interact with synapses, engaging a bi-directional communication critical for the processing of synaptic information (Ben Achour and Pascual, 2010; Henneberger et al., 2010; Ragozzino et al., 2006; Rogers et al., 2011), recent evidence has proposed microglia as key players in the normal regulation of synaptic plasticity. This has led to the concept of a “quad-partite synapse” (Schafer et al., 2013), suggesting that, not only astrocytes and pre- and post-synaptic elements can function together as an interdependent unit to regulate synaptic function and plasticity (“tripartite synapse”) (Araque et al., 1999), but that also microglia can interact with synapses in a regulatory and responsive manner (Schafer et al., 2013). This concept is supported by the observations that patients with depression have a decreased density and hypofunction of astrocytes (Cotter et al., 2002; Cotter et al., 2001), as well as an increased microglial “activation” in distinct brain regions, like prefrontal cortex, anterior cingulate cortex and insula, which are often involved in the clinical manifestation of the depressive symptomatology (Setiawan et al., 2015).

Furthermore, the traditional culprits of depression (inflammation, glucocorticoids and reduced brain-derived neurotrophic factor (BDNF)) affect astrocyte and microglia functioning, whereas antidepressant treatments (serotonin-selective reuptake inhibitors (SSRIs), electroshocks, cognitive behavioural therapy) recover astrocyte and microglia functioning (Li et al., 2018; Tynan et al., 2012; Zhang et al., 2009), therefore proposing microglia dysfunction as one of the main determinants in the regulation of synaptic plasticity in the context of MDD.

In particular, microglia could affect synaptic plasticity in models of depression via impairment of distinct molecular mechanisms regulating both LTP and LTD (Liu et al., 2015b; Milior et al., 2016; Riazi et al., 2015). CX<sub>3</sub>CR1, a microglia specific receptor for the chemokine fractalkine in the CNS has been shown to mediate physiological modification of synaptic plasticity (Ragozzino et al., 2006; Rogers et al., 2011), with CX<sub>3</sub>CR1 knockout studies reporting a clear resistance to the development of depressive-like behaviour and antidepressant treatment in animals (Hellwig et al., 2016; Milior et al., 2016; Rimmerman et al., 2017). Since microglia are the primary immune cells of the brain, it is also unsurprising that microglial production of inflammatory cytokines, including interleukin-1 beta (IL-1 $\beta$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ ) have been shown to impair LTP in models of depression (Liu et al., 2015b). The effects of microglial-derived IL-1 $\beta$  and TNF- $\alpha$  on LTP are diverse, including reductions in AMPA receptor phosphorylation (Liu et al., 2015b) and modification of NMDA and AMPA receptor subunit expression (Riazi et al., 2015).

Furthermore, microglia are important trophic supporters of neurons through production of the brain derived neurotrophic factor (BDNF) (Ferrini and De Koninck, 2013), whose expression levels have shown to be significantly altered in MDD patients (Zhang et al., 2014b). Interestingly, in the context of synaptic plasticity, microglial BDNF has been shown to influence the levels of specific proteins, like glutamate receptor subunit epsilon-2 (GluN2B) and vesicular glutamate transporter 1 (VGlut1), which are involved in the regulation of glutamatergic synaptic function (Parkhurst, 2013), therefore suggesting a potential involvement of BDNF as a mediator of microglial-dependent changes in synaptic plasticity.

Recruitment and activation of microglia has also been argued to occur through ATP P2X purinoceptor 7 (P2XR7) (Bennett et al., 2009), whose expression, together with BDNF, has shown to be altered in patients with depression (Bennett, 2007). Models of MDD have

identified P2X7 as an important contributor to cytokine production, which in turns could drive changes in synaptic plasticity and LTP impairments (Yue et al., 2017). Furthermore, microglia are significant contributors to reactive oxygen species (ROS) production in the CNS. The modification of microglial activity in MDD models has been shown to facilitate increased ROS release from microglia (Seo et al., 2012), which is known to impair synaptic plasticity and facilitate novel forms of LTD (Zhang et al., 2014a).

Overall, this evidence supports the hypothesis that microglial-dependent modification of synaptic plasticity might be relevant in the context of MDD and therefore it worth extensive analysis. Whilst the effects of altered inflammation and microglial activity on many aspects of neuronal function in the context of MDD have been the subject of previous reviews (Yirmiya et al., 2015), here we discuss the putative role of inflammation and microglial activity in the regulation and modification of synaptic plasticity, in the context of MDD.

### **Microglial modification of synaptic plasticity in MDD**

#### *Fractalkine (CX<sub>3</sub>CL1)- and CX<sub>3</sub>CR1- mediated microglial modification of LTP*

Fractalkine has been proposed as a critical modifier of microglial activity in MDD (Rimmerman et al., 2017). Fractalkine and its corresponding receptor CX<sub>3</sub>CR1 have shown to regulate synaptic phagocytosis, impair LTP, and ultimately to cause changes in hippocampal structure and function (Milior et al., 2016). This evidence primarily comes from chronic unpredictable stress (CUS) mouse models of MDD. In particular, CX<sub>3</sub>CR1 knockouts mice displayed resistance to depressive-like behaviours compared to wild-type controls (Milior et al., 2016), potentially due to microglial-dependent modifications. Interestingly, when assessing microglia the authors reported increased phagocytic inclusions of pre-synaptic axon



terminals and post-synaptic dendritic spines in the CA1 hippocampal output region of CUS exposed wild-type mice, but not in CX<sub>3</sub>CR1 knockouts (Mili<sup>or</sup> et al., 2016). This is in accordance with previous data showing reduced spine density in rat hippocampal neurons, in an olfactory bulbectomy model of depression (Norrholm and Ouimet, 2001).

Although CUS was shown to alter short term plasticity in wild-type mice only, high frequency stimulation-induced LTP was impaired in both wild-type and CX<sub>3</sub>CR1 knockout mice (Mili<sup>or</sup> et al., 2016). Importantly, CUS only impaired further attempts to induce LTP in wild-type mice, with CUS causing LTP saturation after a second stimulation protocol, and contributing to reductions in synaptic weighting (Mili<sup>or</sup> et al., 2016). This evidence has been used to suggest the possibility that in CUS models of MDD, microglial phagocytosis of pre-synaptic axon terminals and post synaptic dendrites can contribute to impaired neuronal LTP (Mili<sup>or</sup> et al., 2016) (see Figure 1).

This hypothesis is supported by *in vitro* experiments on rat CA1 hippocampal neurons identifying an "all-or-nothing" feature to LTP at an individual synaptic level, which would imply new synapses are required for further LTP induction (Petersen et al., 1998). An alternative explanation for how microglia could cause an early LTP saturation arise from the identification of AMPA receptor lacking "silent synapses", which become active by expressing AMPA receptors following LTP induction (Kerchner and Nicoll, 2008; Liao et al., 1995). As microglia have been shown to phagocytose synapses following CUS exposure, elimination of "silent synapses" by microglia would make them unavailable for activation and LTP induction. Therefore, microglial elimination of "silent synapses" in CUS exposed mice might have prevented neurons from undergoing subsequent episodes of LTP (Mili<sup>or</sup> et al., 2016), by reducing the number of newly available active synapses for LTP (see Figure 1).

Although, the role for fractalkine in synaptic plasticity is supported by evidence that CX<sub>3</sub>CR1 knockout mice display increased hippocampal spine densities in the developing brain (Paolicelli et al., 2011), the presence of altered microglial morphology is not consistent across studies of CX<sub>3</sub>CR1 and MDD. In a chronic despair model of depression, CX<sub>3</sub>CR1 knockout mice were shown to possess resistance to depressive-like behaviour, whilst wild-type mice microglia were shown to possess a reactive morphology as opposed to CX<sub>3</sub>CR1 knockouts (Hellwig et al., 2016). Another study of CX<sub>3</sub>CR1 knockout mice exposed to CUS demonstrated resistance to depressive-like behaviours, with both control and knockout mice having reduced microglia process lengths (Rimmerman et al., 2017). Furthermore, CX<sub>3</sub>CR1 knockout microglia have larger soma areas than wild types, indicating that CX<sub>3</sub>CR1 absence can alter microglial shape (Rimmerman et al., 2017). These findings demonstrate that just as fractalkine signalling can be heterogenous in altering synaptic plasticity (Ragozzino et al., 2006; Rogers et al., 2011), elimination of CX<sub>3</sub>CR1 through knockouts results in a considerable variation of microglial morphology. This heterogeneity requires further investigation to ascertain the importance of microglial morphology to mediating changes in synaptic function and in MDD.

Whilst structural modification of synapses mediated by CX<sub>3</sub>CR1 can potentially modulate synaptic plasticity in MDD, there are alternative mechanisms fractalkine signalling can influence to impair LTP. Stimulation of microglia with fractalkine has been shown to inhibit LTP in mice, following high frequency stimulation of schaffer collaterals synapsing with CA1 neurons, which did not occur in CX<sub>3</sub>CR1 knockout mice (Maggi et al., 2009). Interestingly, application of a protein phosphatase A1 (PPA1) and PPA2 inhibitor prevented fractalkine-mediated impairment of LTP induction (Maggi et al., 2009). This finding is supported by previous work on rat CA1 hippocampal neurons, where synaptic depression by

fractalkine exposure was shown to reduce spontaneous excitatory post synaptic currents and to inhibit AMPA receptor GluR1 subunits phosphorylation (Ragozzino et al., 2006).

Finally, the effects of fractalkine on synaptic plasticity were shown to occur via regulation of the A<sub>3</sub> adenosine receptor 3 (A<sub>3</sub>R). Although exposure of A<sub>3</sub>R knockout mice to fractalkine did not affect LTP, exposure of A<sub>1</sub>R and A<sub>2A</sub>R knockout mice hippocampal slices to fractalkine impaired LTP induction (Maggi et al., 2009). Furthermore, similar studies in A<sub>3</sub>R knockout mouse CA1 hippocampal neurons corroborate findings that A<sub>3</sub>R activation depresses AMPA current amplitude (Di Angelantonio et al., 2015). Accordingly, application of an A<sub>3</sub>R antagonist resulted in larger amplitude excitatory post synaptic currents and greater phosphorylation of GluR1 AMPA receptors, which was inhibited by protein kinase A (PKA) antagonists (Di Angelantonio et al., 2015). This is of interest as the nonspecific adenosine receptor antagonist caffeine has been shown to promote PKA signalling in the mouse retina (Ferreira et al., 2014) and to possess antidepressant properties in both human (Wang et al., 2016) and animal models of depression (Pechlivanova et al., 2012). Whilst the effects of caffeine on PKA have not been directly observed in studies of MDD, the improvement of depressive symptoms and regulation of PKA presents an intriguing explanation for a therapeutic mechanism of adenosine in MDD.

#### *Fractalkine-mediated microglial modification of LTD*

As CX<sub>3</sub>CR1 knockout studies and impairment of fractalkine signalling have shown that fractalkine signalling pathways can impair LTP through modification of microglial activity in models of MDD (Milić et al., 2016), it seems relevant to assess how microglia could also potentially influence LTD via the same signalling pathway. It was demonstrated that exposure to fractalkine, in mouse hippocampal neurons is able to induce a depression in excitatory post

synaptic currents that is prevented by application of a fractalkine antibody or knockout of CX<sub>3</sub>CR1 (Bertollini et al., 2006) (see Figure 2). This depression was shown to be a post-synaptic event, as paired pulse ratios were unchanged with fractalkine exposure. Interestingly, fractalkine driven synaptic depression was shown to share mechanisms with LTD, as low frequency stimulation of hippocampal collateral synapses prevented subsequent fractalkine-induced synaptic depression (Bertollini et al., 2006).

Similar studies of fractalkine-related post synaptic depression in rat hippocampal slices have also shown that synaptic depression is mediated by extracellular calcium entry (Ragozzino et al., 2006). Importantly, fractalkine dependent calcium entry was shown to specifically depress AMPA receptor mediated inward currents (Ragozzino et al., 2006). In particular, there was a notable relationship between AMPA receptor currents and synaptic depression, with the degree of fractalkine induced depression appearing to be proportional to the initial amplitude of the AMPA receptor inward current (Ragozzino et al., 2006). In particular, fractalkine-driven synaptic depression was attributed to reductions in adenylate cyclase and cyclic-AMP (cAMP) signalling, which ultimately disrupted PKA and proteins phosphatase activity, as well as GluR1 phosphorylation (Ragozzino et al., 2006) (see Figure 2). This is interesting in the context of MDD as one of the noted effects of antidepressants fluoxetine and tianeptine is an increase in phosphorylation of GluR1 subunits (Svenningsson et al., 2007).

Finally, other research has shown that fractalkine dependent synaptic depression is also mediated by adenosine receptors (Piccinin et al., 2010), and that microglia might be the source of adenosine release from fractalkine (Lauro et al., 2008) (see Figure 2). Interestingly, experiments assessing brain development using CX<sub>3</sub>CR1 knockout mice have identified enhanced LTD only in early postnatal mouse neurons, but not in older neurons (Paolicelli et

al., 2011). Therefore, this finding seems to suggest that the effects of fractalkine signalling on plasticity are likely to vary depending on brain maturation, which would be relevant when comparing MDD patients of different ages.

### *Inflammation-mediated microglial modification of LTP*

Whilst CX<sub>3</sub>CR1 can influence microglial modification of synaptic plasticity, so too can inflammatory cytokines which are known to be elevated in MDD (Dowlati et al., 2010). Indeed, cytokines alone can influence neuronal function as it has been observed in hippocampal progenitor cell lines exposed to inflammatory cytokines including interferon-alpha (IFN- $\alpha$ ) and IL-1 $\beta$ , which can detrimentally affect neurogenesis independent of microglial presence (Borsini et al., 2017a; Borsini et al., 2017b; Zunszain et al., 2012). Furthermore, studies assessing IFN- $\alpha$ -induced depression in humans have identified IFN- $\alpha$  dependent alterations in the expression of genes involved in the regulation of neuroplasticity (Hepgul et al., 2016). Interestingly, differences in neuroplasticity genes expression after four weeks of IFN- $\alpha$  treatment were found to be predictive of patient susceptibility to later development of depression (Hepgul et al., 2016), demonstrating a potential relationship between cytokines, depression, neuronal function and plasticity in humans.

Indeed, ample evidence demonstrates that immune processes in the brain produce detrimental effects on neural plasticity (Goshen et al., 2007; Yirmiya and Goshen, 2011). Previous evidence demonstrated that those immune proteins can reduce hippocampal LTP induction and maintenance (O'Connor and Coogan, 1999). However, in 1998 Hugo Besedovsky and his colleagues reported for the first time that, the secretion of the pro-inflammatory cytokine IL-1 in the hippocampus accompanies LTP induction but not inhibition, and that this cytokine is indeed critically involved in maintaining LTP (Schneider et al., 1998).

Since then, many additional studies verified the role of inflammatory cytokines and other inflammatory mediators in normal, physiological neural plasticity (Yirmiya and Goshen, 2011). Although inflammatory cytokines have been shown to modify both LTP and LTD, studies assessing the effects of inflammatory cytokines in MDD models have primarily focused on the effects of LTP and not LTD.

Previous evidence, using inflammatory models of depression, has shown that an increase in circulating levels of cytokines in response to the inflammatory challenge lipopolysaccharide (LPS) can influence microglial production of TNF- $\alpha$  and IL-1 $\beta$  (Hines et al., 2013), which in turns can detrimentally affect LTP patterns of synaptic activity. Similar to LPS, CUS has also been shown to mediate microglial-dependent production of TNF- $\alpha$  and IL-1 $\beta$ , whose presence contributed to the development of cognitive impairments in animals and to disruption in normal LTP activity (Liu et al., 2015b). In particular, CUS-mediated increase in TNF- $\alpha$  and IL-1 $\beta$  were shown to cause impaired memory performance, in water maze testing, alongside reduced LTP induction, from high frequency stimulation, in rat hippocampal slices. In particular, immunoassays of postsynaptic AMPA receptors showed that the CUS mediated impairment of LTP was associated with reduced phosphorylation of AMPA receptor GluR1 subunits (Liu et al., 2015b). This was demonstrated to be microglia dependent, as administration of microglial inhibitor minocycline during CUS exposure prevented increases in TNF- $\alpha$  and IL-1 $\beta$ , as well as impairment of LTP and AMPA GluR1 phosphorylation (Liu et al., 2015b) (see Figure 3). These findings are highly relevant in the context of MDD, where indeed animal models of depression have shown anti-depressant properties of minocycline in mice exposed to an immune challenge with the cytokine IFN- $\alpha$  (Zheng et al., 2015).

While CUS can impair LTP via microglial activation, peripheral inflammation has also been shown to modify microglial activity and impair LTP independently of stressful stimuli. In a rat model of inflammatory colitis, microglial activation by peripheral inflammation has

been shown to reduce LTP induction in the hippocampus (Riazi et al., 2015). When investigating the mechanisms, these synaptic changes were found to be associated with a reduction in the ratio of AMPA to NMDA receptors, implicating an increase in the NMDA receptor dependent component to post-synaptic current changes relative to AMPA receptors (Riazi et al., 2015). Importantly, the use of minocycline, as an inhibitor of microglial activation, prevented colitis induced reductions in LTP without affecting the severity of colitis. This occurred alongside reductions in hippocampal TNF- $\alpha$  concentrations, implicating a microglia dependent mechanism of impaired LTP potentially mediated by TNF- $\alpha$  (Riazi et al., 2015). Similarly, AMPA receptor GluR2 subunits were also found to be reduced, with the specific GluR2 subunit lacking AMPA receptor antagonist being significantly more effective at impairing excitatory post-synaptic currents in colitis rat neurons (Riazi et al., 2015).

In the inflammatory colitis model, it was also noted that, changes in NMDA dependent signalling, putatively mediated by microglial activation, were associated with reduced glutamate N-methyl D-aspartate receptor subtype 2B (NR2B) subunit expression (Riazi et al., 2015). Indeed, NR2B subunit has been shown to be a crucial component for LTP induction (Muller et al., 2009), therefore supporting findings in colitis rats for the involvement of NR2B in regulating LTP activity. Interestingly, a similar colitis model was also shown to induce behavioural despair and depressive-like behaviours in mice, proposing this model as a relevant example of inflammation-induced depression, where LTP might be one of the mechanisms mediating the relationship between inflammation-dependent microglial activation and subsequent development of depression (Heydarpour et al., 2016).

### *BDNF-mediated microglial modification of LTP*

Whilst the role of microglial cytokines have been briefly discussed, microglial production of BDNF has also been implicated in mediating microglial support for synapses (Parkhurst, 2013). In particular, microglial BDNF has been most clearly shown to mediate modifications to glutamatergic neurotransmission and structural plasticity (Parkhurst, 2013), in a similar manner to neuronal BDNF inducing changes to structural plasticity and LTP (Rex et al., 2007). Although evidence suggests that BDNF is primarily produced by neurons (Dieni et al., 2012), it is argued that microglial and astrocytic BDNF is also important, particularly when focussing at synaptic level (Song et al., 2017).

Furthermore, there is growing interest in the involvement of BDNF in many neuropsychiatric conditions (Autry and Monteggia, 2012; Cattaneo et al., 2016a), where a reduction in its concentration in peripheral blood of patients has been observed (Yoshida et al., 2012). In a mouse model of inflammation-induced depression, mice exposed to LPS displayed depressive-like behaviours, as well as altered concentrations of BDNF in the brain (Zhang et al., 2014b). Although the study found a reduction in BDNF expression and dendritic spine density in the hippocampus and prefrontal cortex, opposite results were found in the nucleus accumbens. This occurred alongside reduced phosphorylation and activation of BDNF receptor tropomyosin receptor kinase B (TrkB) in the hippocampus. This altered BDNF activity was shown to be relevant in the context of MDD, as application of a TrkB agonist reversed depressive behaviours in LPS exposed mice and prevented reductions in spine densities in both the hippocampus and prefrontal cortex (Zhang et al., 2014b).

Whilst microglial activation was not directly assessed in the previous study, depletion of microglial BDNF and subsequent reduction in TrkB phosphorylation in mice has been shown to result in impaired learning and synaptic plasticity (Parkhurst, 2013) (see Figure 4).



Interestingly, reduced TrkB phosphorylation was associated with a reduction in excitatory post synaptic current frequency affecting both AMPA and NMDA receptor contributions. A finding which was correlated with reduced expression of VGlut1, indicative of potential reductions in pre-synaptic glutamate release (Parkhurst, 2013). However, there was also a significant reduction in NMDA decay times of excitatory post-synaptic currents compared to controls, potentially due to reductions in NR2B expression (Parkhurst, 2013), which together with TrkB signalling, has been argued to be an important contributor to LTP and memory formation (Halt et al., 2012; Minichiello, 2009; Mizuno et al., 2003).

#### *ATP-mediated microglial modification of LTP*

One proposed mechanism to explain how microglia are recruited to synapses and can modify synaptic function in MDD is via ATP signalling and the P2X7 regenerative loop model (Bennett et al., 2009). The P2X7 model describes a neuron-glia relationship where low frequency presynaptic neuronal firing releases glutamate, which binds to post-synaptic AMPA and NMDA receptors as well as astrocytic AMPA receptors, causing an increase in intracellular calcium and subsequent release of ATP (Bennett et al., 2009; Queiroz et al., 1997). In the P2X7 model, it is argued that prolonged astrocyte stimulation and release of ATP activates presynaptic neuronal P2X7 receptors, increasing basal calcium concentrations and facilitating greater glutamate release. Moreover, ATP released from astrocytes can also act to attract surveying microglia via activation of P2X7 receptors (Bennett et al., 2009; Honda et al., 2001). This in turn might contribute to the release of cytokines, like TNF- $\alpha$ , which might enhance astrocytic AMPA receptors, post-synaptic AMPA and NMDA receptors, and increase pre-synaptic glutamate release (Bennett et al., 2009).

The P2X7 regenerative loop model of microglial contribution to synaptic regulation is very interesting to explore particularly in the context of MDD (Bennett, 2007), as P2X7 mutations have been identified in human genetic studies of depression (Lucae et al., 2006), and P2X7 knockout mice have been shown to possess antidepressant properties compared to wild types (Basso et al., 2009). One of the possible ways through which microglial P2X7 regulates synaptic plasticity in the context of depression might be through cytokines production. Indeed, previous evidence has shown that *in vitro* treatment of mice microglia with a P2X7 agonist (BzATP) and LPS, can increase distinct cytokines, including TNF- $\alpha$  and IL-1 $\beta$  (He et al., 2017), which have been previously identified for their ability to impair synaptic plasticity, including LTP activity in a CUS model of MDD (Liu et al., 2015b) (see Figure 5). This is important as evidence supporting the production of IL-1 $\beta$  mediated by P2X7 in MDD has also been performed using CUS in rats (Yue et al., 2017). Of note is the fact that P2X7 antagonists were shown to prevent depressive-like behaviours, whilst conversely P2X7 agonists were shown to induce said behaviours (Yue et al., 2017).

Whilst astrocyte mediated regulation of microglia can potentially induce synaptic changes via inflammatory signalling, it is our aim to acknowledge the effects microglia can have on astrocytes to alter synapse function. Indeed, there is also evidence for microglia to influence astrocytic activity via ATP release (Ben Achour and Pascual, 2010; Pascual et al., 2012). *In vitro* evidence has shown that treatment of mouse hippocampal slices with LPS induces transient and astrocyte mediated increase in the frequency of excitatory post synaptic currents (Pascual et al., 2012). Interestingly, this effect was shown to be mediated by the metabotropic glutamate receptor 5 (mGluR5) (Pascual et al., 2012). In the context of MDD, mGluR5 is of particular interest, as mGluR5 antagonists (like MTEP) have been shown to possess antidepressant properties (Palucha et al., 2005). Furthermore, the antidepressant properties of MTEP have been shown in an astroglial degeneration model of depression, where

there is a proposed increase in extracellular glutamate, due to reduced astrocytic uptake (Domin et al., 2014). Therefore, development of novel therapeutics which target ATP signalling or P2X7 receptors may be beneficial in regulating microglial recruitment to synapses or microglia-astrocyte signalling, and may prevent pathological modification of LTP to treat MDD symptoms.

#### *Oxidative stress-mediated microglial modification of LTD*

Finally, ROS production is one of the central components of microglial function. From use in immune protection of the brain and elimination of pathogenic threats to redox signalling, ROS are critical to normal immune function in the central nervous system (Vilhardt et al., 2017). Due to the potential harm ROS can cause to neurons, there is a careful balance between microglial ROS and antioxidant production to facilitate normal brain function (Vilhardt et al., 2017), which can be disrupted in MDD (Bakunina et al., 2015). In rodent models of depression, ROS have been implicated in mediating pathological changes in the hypothalamic-pituitary-adrenal axis (Schiavone et al., 2013), as well as impairing normal neuronal functions such as neurogenesis and facilitating neuronal death (Bakunina et al., 2015).

Research into the effects of persistent pain states in the spinal cords of rats has shown that ROS have the ability to induce LTP in an overlapping manner to NMDA activation through high frequency stimulation protocols (Lee et al., 2010). Furthermore, in the context of MDD, exposure of rats to a chronic mild stress model of MDD has been shown to cause increased microglial activation and production of ROS compared to controls (Liu et al., 2015a). In this study, increases in ROS were also associated with an increase in nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) p65 and inducible nitric oxide synthase mRNA expression. Likewise, there were notable reductions in super oxide dismutase (SOD)

expression, showing that chronic mild stress can disrupt the delicate balance between ROS and antioxidant enzymes in favour of ROS (Liu et al., 2015a).

One way in which microglial production of ROS can potentially impair memory formation and cognitive function in MDD is via pathological induction of LTD. Concomitant hypoxia and LPS exposure to rat hippocampal slices has been shown to induce LTD via a microglial complement receptor 3 dependent mechanism (Zhang et al., 2014a). Induction of LTD was shown to be dependent on microglial NADPH oxidase, a producer of superoxide, which when inhibited with the antagonist apocynin, prevented LPS-hypoxia driven LTD (Zhang et al., 2014a) (see Figure 6). Interestingly, NADPH oxidase has been shown to mediate depressive-like behaviours in chronic restraint stressed mice which was prevented by administration of apocynin (Seo et al., 2012). Finally, closer assessment of LPS-hypoxia induced LTD revealed that NADPH oxidase activity was affected by elevated lactic acid secondary to hypoxic conditions. Indeed, application of lactic acid with LPS induced the same LTD seen in hypoxia and was blocked by apocynin (Zhang et al., 2014a) (see Figure 6). This is interesting as MRI imaging data has shown adolescent patients with MDD under normal physiological conditions to display higher levels of ventricular lactate than healthy controls (Bradley et al., 2016). Moreover, LPS-hypoxia dependent LTD was shown to be mediated by GluR2 dependent AMPA receptor endocytosis, but not by regulation of NMDA receptors (Zhang et al., 2014a) (see Figure 6). This is of note as normally LTD synaptic patterns are mediated by NMDA or metabotropic glutamate receptors, perhaps suggesting the presence of a unique form of LTD in the presence of ROS.

## Conclusions and Future Directions

This review highlights the important role microglia can play in modulation of synaptic plasticity and the ways it can translate into altered synaptic plasticity in MDD. Here we present a putative argument for fractalkine dependent modulation of microglial phagocytosis that can result in an early saturation point for LTP. We also discuss how fractalkine driven impairment of LTP via adenosine signalling and facilitation of LTD can potentially contribute to changes in normal synaptic function. Likewise, we have also shown how microglial production of inflammatory cytokines in MDD could drive impairments to LTP by reducing AMPA receptor phosphorylation, and how stimulation of microglia by systemic inflammation can alter NMDA receptor function. We have addressed how MDD mediated impairment of BDNF production in microglia can alter TrkB phosphorylation and how this can impair pre- and post-synaptic glutamate neurotransmission. Furthermore, we have discussed the importance of microglia-astrocyte communication via ATP and how this can alter synaptic function in the context of MDD by increasing IL-1 $\beta$  production and by activating metabotropic glutamate receptors. Finally, we have presented an argument for microglial production of reactive oxygen species driving a novel form of LTD, independent of NMDA receptor and metabotropic glutamate receptor LTD, that can potentially contribute to altered synaptic plasticity in MDD.

Understanding how synaptic plasticity is altered in MDD and how microglia contribute to these changes is important as altered plasticity in MDD could be used to explain observations that patients with treatment resistant depression have positive responses to neuronal stimulation (Bliss and Cooke, 2011). In particular, electroconvulsive therapy (ECT) and rTMS have been shown to be of benefit to some patients with treatment resistant depression, with rTMS possessing the added benefit to ECT of reporting minimal side effects (Fitzgerald et al., 2006). Stimulation from ECT as well as rTMS have been hypothesised to potentially mediate reductions in aberrant cortical excitability (Bliss and Cooke, 2011), supporting the concept of

targeting, or preventing changes to synaptic plasticity in MDD directly. Indeed, it has been shown that electroconvulsive stimulation in rats induces increased expression of LTD related proteins which could reduce MDD dependent neuronal excitability (Kato, 2009), demonstrating the potential therapeutic benefits that can be gained from modifying synaptic plasticity to treat MDD.

Currently our ability to monitor microglial activity in the human brain is limited. Using TSPO markers in positron emission tomography (PET), it is possible to generate statistical variations in regional microglial activity (Vivash and O'Brien, 2016), however this is impractical in the routine diagnostics of MDD. As such, TSPO dependent PET imaging is currently inadequate at creating a detailed understanding of microglial activity in MDD. Therefore, an easier way would be that of performing initial assessment of peripheral inflammatory markers, such as TNF- $\alpha$  and IL-1 $\beta$  to identify an immune dependent form of MDD, which microglia can likely be influenced by. Indeed, the use of human inflammatory profiles to assess predictors of antidepressant treatment response has already identified IL-1 $\beta$  and macrophage migration inhibitory factor (MIF) as potential contributors of non-responsiveness to the SSRI escitalopram and the tricyclic nortryptilline (Cattaneo et al., 2016b). Furthermore, network analysis of the effects of MIF has established interactions with genes involved in the regulation of neurogenesis, neuroplasticity and cellular proliferation, which could contribute to altered synaptic plasticity in MDD (Cattaneo et al., 2016b). This should be combined with current knowledge regarding contributing factors to MDD, including genetics (Bufalino et al., 2013; Lucae et al., 2006) and concurrent pathological conditions, which will drive a better understanding of the MDD spectrum and identify where microglia would fit into that spectrum. This may be particularly beneficial for clinicians when selecting therapeutic options, as differing SSRIs, such as venlafaxine and sertraline, have been shown to promote respectively anti-inflammatory and pro-inflammatory cytokine production in hippocampal

progenitor cell lines, which could ultimately enhance or mitigate microglial activity (Horowitz et al., 2014).

Although impractical in clinical MDD assessments, TSPO does have the potential to provide an initial insight into the role of microglial modification of plasticity in human MDD studies. By combining TSPO imaging with rTMS, it may be possible to identify areas of the brain which display an increased level of microglial activity and altered plasticity to provide correlative evidence supporting microglial involvement in impaired plasticity in MDD. Developing an understanding of microglial dependent altered plasticity in MDD may help to explain why some patients with treatment resistant depression respond to therapies such as rTMS (Fitzgerald et al., 2006) and ECT (Folkerts et al., 1997). Furthermore, this would support the development of more specific therapeutic targets for microglia to prevent changes to plasticity.

Currently, targeting microglial function with focused therapies is difficult to achieve in human studies. Therefore, inhibition of microglial activity with non-specific drugs, such as minocycline are being investigated for their potential benefits in depression management (Dean et al., 2017). However, microglial activity is complex, consisting of both inflammatory and neuro-supportive actions which are important in normal brain physiology (Mantovani et al., 2004). As such, unfocused inhibition of microglia is not sufficient to address all the changes to microglial function that occur in MDD.

Historically, microglia have been categorised as either M1 proinflammatory reactive phenotypes, which inhibit plasticity or M2 supportive phenotypes, which facilitate synaptic plasticity (Lynch, 2015). Furthermore, this concept of M1 and M2 microglia has driven the idea of inhibiting inflammatory microglia and promoting more supportive phenotypes to manage diseases in the brain (Cherry et al., 2014). However, this perspective has shifted and

microglial activity is now viewed as a spectrum of both inflammatory and neuron supporting actions, which are dependent on many factors including location within the brain and the stimuli microglia are exposed to (Ransohoff, 2016). Therefore, simply inhibiting microglial activity is unlikely to treat microglia driven pathology and alterations in synaptic plasticity. Future efforts should be focused towards developing new ways of regulating microglia, via suppressing any over active inflammatory responses and therefore facilitate the restoration of physiological microglial regulation of synapses.

As current methods for targeting microglia themselves are limited, focusing on the by-products of microglial activity could be useful in developing therapeutics to treat MDD and restore changes to plasticity. Novel therapies addressing microglial ROS production and balance could be used alongside standard MDD therapies to manage ROS-induced depressive changes. Indeed, elevated oxidative stress have been indicated as a significant biomarker in non-SSRI responding MDD patients (Lindqvist et al., 2017). Furthermore, although there has been conflicting data regarding supplementation with antioxidants (Sahraian et al., 2015), administration of ascorbic acid or omega-3 fatty acids have been argued to be effective in preventing MDD symptoms (Chang et al., 2017; Su et al., 2010; Su et al., 2014), and in reducing ROS (Balmus et al., 2016). Targeting ROS activity could hamper microglial modification of synaptic plasticity by inhibiting ROS induced LTD (Zhang et al., 2014a) and facilitate the restoration of normal neuronal function in MDD. Likewise, neuroprotective factors like BDNF have been linked to antidepressant efficacy, specifically in the effectiveness of SSRIs in rats exposed to CUS (Ibarguen-Vargas et al., 2009). Therefore, modulation of BDNF pathways, alongside current antidepressant therapies has the potential to support management of MDD (Berton and Nestler, 2006; Zhang et al., 2016). By supplementing or promoting microglial production of BDNF it may be possible to prevent changes to synaptic



plasticity which could contribute to both MDD symptoms and impaired responsiveness to conventional antidepressant therapies.

Overall this compilation of evidences illustrates the relevance of those mechanisms in the control of neuron-glia bidirectional communication and their therapeutic potential in the normalization of aberrant synaptic processing in the context of depression. Future research should aim at developing a greater understanding of changes to LTP and LTD in depression, particularly in relation to microglial activity, which will provide new insights on the dynamics occurring at a cellular level in MDD patients, as well as contribute to the development of new exciting therapeutic options for the treatment of MDD in the future.

**Acknowledgments:** Dr Borsini have received research funding by the Medical Research Council (UK) (grant MR/N029488/1) and by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Professor Pariante has funded by the UK National Institute for Health Research (NIHR) Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London, the UK Medical Research Council (grants MR/L014815/1, MR/J002739/1 and MR/N029488/1) and the Psychiatry Research Trust.

## References:

- Araque, A., Parpura, V., Sanzgiri, R.P., Haydon, P.G., 1999. Tripartite synapses: glia, the unacknowledged partner. *Trends Neurosci* 22, 208-215.
- Autry, A.E., Monteggia, L.M., 2012. Brain-Derived Neurotrophic Factor and Neuropsychiatric Disorders, *Pharmacol Rev*, pp. 238-258.
- Bakunina, N., Pariante, C.M., Zunszain, P.A., 2015. Immune mechanisms linked to depression via oxidative stress and neuroprogression. *Immunology* 144, 365-373.
- Balmus, I.M., Ciobica, A., Antioch, I., Dobrin, R., Timofte, D., 2016. Oxidative Stress Implications in the Affective Disorders: Main Biomarkers, Animal Models Relevance, Genetic Perspectives, and Antioxidant Approaches. *Oxid Med Cell Longev* 2016, 397-341.
- Basso, A.M., Bratcher, N.A., Harris, R.R., Jarvis, M.F., Decker, M.W., Rueter, L.E., 2009. Behavioral profile of P2X7 receptor knockout mice in animal models of depression and anxiety: relevance for neuropsychiatric disorders. *Behav Brain Res* 198, 83-90.
- Ben Achour, S., Pascual, O., 2010. Glia: the many ways to modulate synaptic plasticity. *Neurochem Int* 57, 440-445.
- Bennett, M.R., 2007. Synaptic P2X7 receptor regenerative-loop hypothesis for depression. *Aust N Z J Psychiatry* 41, 563-571.
- Bennett, M.R., Farnell, L., Gibson, W.G., 2009. P2X7 regenerative-loop potentiation of glutamate synaptic transmission by microglia and astrocytes. *J Theor Biol* 261, 1-16.
- Bertollini, C., Ragozzino, D., Gross, C., Limatola, C., Eusebi, F., 2006. Fractalkine/CX3CL1 depresses central synaptic transmission in mouse hippocampal slices. *Neuropharmacology* 51, 816-821.
- Berton, O., Nestler, E.J., 2006. New approaches to antidepressant drug discovery: beyond monoamines. *Nat Rev Neurosci* 7, 137-151.
- Bliss, T.V., Collingridge, G.L., 2013. Expression of NMDA receptor-dependent LTP in the hippocampus: bridging the divide, *Mol Brain*, p. 5.
- Bliss, T.V., Cooke, S.F., 2011. Long-term potentiation and long-term depression: a clinical perspective, *Clinics (Sao Paulo)*, pp. 3-17.
- Borsini, A., Alboni, S., Horowitz, M.A., Tojo, L.M., Cannazza, G., Su, K.P., Pariante, C.M., Zunszain, P.A., 2017a. Rescue of IL-1 $\beta$ -induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. *Brain Behav Immun* 65, 230-238.
- Borsini, A., Cattaneo, A., Malpighi, C., Thuret, S., Harrison, N.A., Zunszain, P.A., Pariante, C.M., 2017b. Interferon-Alpha Reduces Human Hippocampal Neurogenesis and Increases Apoptosis via Activation of Distinct STAT1-Dependent Mechanisms. *Int J Neuropsychopharmacol*.
- Bradley, K.A.L., Mao, X., Case, J.A.C., Kang, G., Shungu, D.C., Gabbay, V., 2016. Increased Ventricular Cerebrospinal Fluid Lactate in Depressed Adolescents. *Eur Psychiatry* 32, 1-8.
- Bufalino, C., Hepgul, N., Aguglia, E., Pariante, C.M., 2013. The role of immune genes in the association between depression and inflammation: a review of recent clinical studies. *Brain Behav Immun* 31, 31-47.
- Cantone, M., Bramanti, A., Lanza, G., Pennisi, M., Bramanti, P., Pennisi, G., Bella, R., 2017. Cortical Plasticity in Depression: A Neurochemical Perspective From Transcranial Magnetic Stimulation, *ASN Neuro*, pp. 175-180.
- Cattaneo, A., Cattane, N., Begni, V., Pariante, C.M., Riva, M.A., 2016a. The human BDNF gene: peripheral gene expression and protein levels as biomarkers for psychiatric disorders, *Transl Psychiatry*, pp. e958-.
- Cattaneo, A., Ferrari, C., Uher, R., Bocchio-Chiavetto, L., Riva, M.A., Pariante, C.M., 2016b. Absolute Measurements of Macrophage Migration Inhibitory Factor and Interleukin-1 $\beta$  mRNA Levels Accurately Predict Treatment Response in Depressed Patients. *Int J Neuropsychopharmacol* 19.
- Chang, J.P., Lai, H.C., Yang, H.T., Su, W.P., Peng, C.Y., Galecki, P., Walczewska, A., Pariante, C.M., Su, K.P., 2017. Polyunsaturated fatty acids levels and initial presentation of somatic symptoms induced by interferon-alpha therapy in patients with chronic hepatitis C viral infection. *Nutr Neurosci* 20, 291-296.

Cherry, J.D., Olschowka, J.A., O'Banion, M.K., 2014. Neuroinflammation and M2 microglia: the good, the bad, and the inflamed, *J Neuroinflammation*, p. 98.

Collingridge, G.L., Peineau, S., Howland, J.G., Wang, Y.T., 2010. Long-term depression in the CNS. *Nat Rev Neurosci* 11, 459-473.

Cotter, D., Mackay, D., Chana, G., Beasley, C., Landau, S., Everall, I.P., 2002. Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cereb Cortex* 12, 386-394.

Cotter, D., Mackay, D., Landau, S., Kerwin, R., Everall, I., 2001. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch Gen Psychiatry* 58, 545-553.

Dale, E., Pehrson, A.L., Jeyarajah, T., Li, Y., Leiser, S.C., Smagin, G., Olsen, C.K., Sanchez, C., 2016. Effects of serotonin in the hippocampus: how SSRIs and multimodal antidepressants might regulate pyramidal cell function, *CNS Spectr*, pp. 143-161.

Dean, O.M., Kanchanatawan, B., Ashton, M., Mohebbi, M., Ng, C.H., Maes, M., Berk, L., Sughondhabirrom, A., Tangwongchai, S., Singh, A.B., McKenzie, H., Smith, D.J., Malhi, G.S., Dowling, N., Berk, M., 2017. Adjunctive minocycline treatment for major depressive disorder: A proof of concept trial. *Aust N Z J Psychiatry* 51, 829-840.

Di Angelantonio, S., Bertollini, C., Piccinin, S., Rosito, M., Trettel, F., Pagani, F., Limatola, C., Ragozzino, D., 2015. Basal adenosine modulates the functional properties of AMPA receptors in mouse hippocampal neurons through the activation of A1R A2AR and A3R. *Front Cell Neurosci* 9.

Dieni, S., Matsumoto, T., Dekkers, M., Rauskolb, S., Ionescu, M.S., Deogracias, R., Gundelfinger, E.D., Kojima, M., Nestel, S., Frotscher, M., Barde, Y.A., 2012. BDNF and its pro-peptide are stored in presynaptic dense core vesicles in brain neurons. *J Cell Biol* 196, 775-788.

Domin, H., Szewczyk, B., Wozniak, M., Wawrzak-Wlecial, A., Smialowska, M., 2014. Antidepressant-like effect of the mGluR5 antagonist MTEP in an astroglial degeneration model of depression. *Behav Brain Res* 273, 23-33.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctot, K.L., 2010. A meta-analysis of cytokines in major depression. *Biol Psychiatry* 67, 446-457.

Ferreira, D.D., Stutz, B., de Mello, F.G., Reis, R.A., Kubrusly, R.C., 2014. Caffeine potentiates the release of GABA mediated by NMDA receptor activation: Involvement of A1 adenosine receptors. *Neuroscience* 281, 208-215.

Ferrini, F., De Koninck, Y., 2013. Microglia Control Neuronal Network Excitability via BDNF Signalling. *Neural Plast* 2013.

Fitzgerald, P.B., Benitez, J., de Castella, A., Daskalakis, Z.J., Brown, T.L., Kulkarni, J., 2006. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry* 163, 88-94.

Folkerts, H.W., Michael, N., Tolle, R., Schonauer, K., Mucke, S., Schulze-Monking, H., 1997. Electroconvulsive therapy vs. paroxetine in treatment-resistant depression -- a randomized study. *Acta Psychiatr Scand* 96, 334-342.

Goshen, I., Kreisel, T., Ounallah-Saad, H., Renbaum, P., Zalzstein, Y., Ben-Hur, T., Levy-Lahad, E., Yirmiya, R., 2007. A dual role for interleukin-1 in hippocampal-dependent memory processes. *Psychoneuroendocrinology* 32, 1106-1115.

Halt, A.R., Dallapiazza, R.F., Zhou, Y., Stein, I.S., Qian, H., Juntti, S., Wojcik, S., Brose, N., Silva, A.J., Hell, J.W., 2012. CaMKII binding to GluN2B is critical during memory consolidation, *EMBO J*, pp. 1203-1216.

He, Y., Taylor, N., Furgeaud, L., Bhattacharya, A., 2017. The role of microglial P2X7: modulation of cell death and cytokine release, *J Neuroinflammation*.

Hellwig, S., Brioschi, S., Dieni, S., Frings, L., Masuch, A., Blank, T., Biber, K., 2016. Altered microglia morphology and higher resilience to stress-induced depression-like behavior in CX3CR1-deficient mice. *Brain Behav Immun* 55, 126-137.

Henneberger, C., Papouin, T., Oliet, S.H.R., Rusakov, D.A., 2010. Long term potentiation depends on release of D-serine from astrocytes. *Nature* 463, 232-236.

Hepgul, N., Cattaneo, A., Agarwal, K., Baraldi, S., Borsini, A., Bufalino, C., Forton, D.M., Mondelli, V., Nikkheslat, N., Lopizzo, N., Riva, M.A., Russell, A., Hotopf, M., Pariante, C.M., 2016. Transcriptomics in Interferon- $\alpha$ -Treated Patients Identifies Inflammation-, Neuroplasticity- and Oxidative Stress-Related Signatures as Predictors and Correlates of Depression, *Neuropsychopharmacology*, pp. 2502-2511.

Herring, B.E., Nicoll, R.A., 2016. Long-Term Potentiation: From CaMKII to AMPA Receptor Trafficking. *Annu Rev Physiol* 78, 351-365.

Heydarpour, P., Rahimian, R., Fakhfour, G., Khoshkish, S., Fakhraei, N., Salehi-Sadaghiani, M., Wang, H., Abbasi, A., Dehpour, A.R., Ghia, J.E., 2016. Behavioral despair associated with a mouse model of Crohn's disease: Role of nitric oxide pathway. *Prog Neuropsychopharmacol Biol Psychiatry* 64, 131-141.

Hines, D.J., Choi, H.B., Hines, R.M., Phillips, A.G., MacVicar, B.A., 2013. Prevention of LPS-induced microglia activation, cytokine production and sickness behavior with TLR4 receptor interfering peptides. *PLoS One* 8, e60388.

Honda, S., Sasaki, Y., Ohsawa, K., Imai, Y., Nakamura, Y., Inoue, K., Kohsaka, S., 2001. Extracellular ATP or ADP induce chemotaxis of cultured microglia through Gi/o-coupled P2Y receptors. *J Neurosci* 21, 1975-1982.

Horowitz, M.A., Wertz, J., Zhu, D., Cattaneo, A., Musaelyan, K., Nikkheslat, N., Thuret, S., Pariante, C.M., Zunszain, P.A., 2014. Antidepressant compounds can be both pro- and anti-inflammatory in human hippocampal cells. *Int J Neuropsychopharmacol* 18.

Ibarguen-Vargas, Y., Surget, A., Vourc'h, P., Leman, S., Andres, C.R., Gardier, A.M., Belzung, C., 2009. Deficit in BDNF does not increase vulnerability to stress but dampens antidepressant-like effects in the unpredictable chronic mild stress. *Behav Brain Res* 202, 245-251.

Kato, N., 2009. Neurophysiological mechanisms of electroconvulsive therapy for depression. *Neurosci Res* 64, 3-11.

Kerchner, G.A., Nicoll, R.A., 2008. Silent synapses and the emergence of a postsynaptic mechanism for LTP. *Nat Rev Neurosci* 9, 813.

Kuhn, M., Mainberger, F., Feige, B., Maier, J.G., Mall, V., Jung, N.H., Reis, J., Klöppel, S., Normann, C., Nissen, C., 2016. State-Dependent Partial Occlusion of Cortical LTP-Like Plasticity in Major Depression, *Neuropsychopharmacology*, pp. 1521-1529.

Lauro, C., Di Angelantonio, S., Cipriani, R., Sobrero, F., Antonilli, L., Brusadin, V., Ragozzino, D., Limatola, C., 2008. Activity of adenosine receptors type 1 is required for CX3CL1-mediated neuroprotection and neuromodulation in hippocampal neurons. *J Immunol* 180, 7590-7596.

Lee, K.Y., Chung, K., Chung, J.M., 2010. Involvement of Reactive Oxygen Species in Long-Term Potentiation in the Spinal Cord Dorsal Horn, *J Neurophysiol*, pp. 382-391.

Li, H., Sagar, A.P., Keri, S., 2018. Translocator protein (18kDa TSPO) binding, a marker of microglia, is reduced in major depression during cognitive-behavioral therapy. *Prog Neuropsychopharmacol Biol Psychiatry* 83, 1-7.

Liao, D., Hessler, N.A., Malinow, R., 1995. Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. *Nature* 375, 400-404.

Lindqvist, D., Dhabhar, F.S., James, S.J., Hough, C.M., Jain, F.A., Bersani, F.S., Reus, V.I., Verhoeven, J.E., Epel, E.S., Mahan, L., Rosser, R., Wolkowitz, O.M., Mellon, S.H., 2017. Oxidative stress, inflammation and treatment response in major depression. *Psychoneuroendocrinology* 76, 197-205.

Liu, B., Xu, C., Wu, X., Liu, F., Du, Y., Sun, J., Tao, J., Dong, J., 2015a. Icariin exerts an antidepressant effect in an unpredictable chronic mild stress model of depression in rats and is associated with the regulation of hippocampal neuroinflammation. *Neuroscience* 294, 193-205.

Liu, M., Li, J., Dai, P., Zhao, F., Zheng, G., Jing, J., Wang, J., Luo, W., Chen, J., 2015b. Microglia activation regulates GluR1 phosphorylation in chronic unpredictable stress-induced cognitive dysfunction. *Stress* 18, 96-106.

Lucae, S., Salyakina, D., Barden, N., Harvey, M., Gagne, B., Labbe, M., Binder, E.B., Uhr, M., Paez-Pereda, M., Sillaber, I., Ising, M., Bruckl, T., Lieb, R., Holsboer, F., Muller-Myhsok, B., 2006. P2RX7, a gene coding for a purinergic ligand-gated ion channel, is associated with major depressive disorder. *Hum Mol Genet* 15, 2438-2445.

Lüscher, C., Malenka, R.C., 2012. NMDA Receptor-Dependent Long-Term Potentiation and Long-Term Depression (LTP/LTD), *Cold Spring Harb Perspect Biol*.

Lynch, M.A., 2004. Long-term potentiation and memory. *Physiol Rev* 84, 87-136.

Lynch, M.A., 2015. Neuroinflammatory changes negatively impact on LTP: A focus on IL-1 $\beta$ . *Brain Res* 1621, 197-204.

MacQueen, G.M., Yucel, K., Taylor, V.H., Macdonald, K., Joffe, R., 2008. Posterior hippocampal volumes are associated with remission rates in patients with major depressive disorder. *Biological psychiatry* 64, 880-883.

Maggi, L., Trettel, F., Scianni, M., Bertollini, C., Eusebi, F., Fredholm, B.B., Limatola, C., 2009. LTP impairment by fractalkine/CX3CL1 in mouse hippocampus is mediated through the activity of adenosine receptor type 3 (A3R). *J Neuroimmunol* 215, 36-42.

Mantovani, A., Sica, A., Sozzani, S., Allavena, P., Vecchi, A., Locati, M., 2004. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol* 25, 677-686.

Milior, G., Lecours, C., Samson, L., Bisht, K., Poggini, S., Pagani, F., Deflorio, C., Lauro, C., Alboni, S., Limatola, C., Branchi, I., Tremblay, M.E., Maggi, L., 2016. Fractalkine receptor deficiency impairs microglial and neuronal responsiveness to chronic stress. *Brain Behav Immun* 55, 114-125.

Minichiello, L., 2009. TrkB signalling pathways in LTP and learning. *Nature Reviews Neuroscience* 10, 850-860.

Mizuno, M., Yamada, K., He, J., Nakajima, A., Nabeshima, T., 2003. Involvement of BDNF Receptor TrkB in Spatial Memory Formation. *Learn Mem* 10, 108-115.

Mondelli, V., Vernon, A.C., Turkheimer, F., Dazzan, P., Pariante, C.M., 2017. Brain microglia in psychiatric disorders. *Lancet Psychiatry* 4, 563-572.

Muller, T., Albrecht, D., Gebhardt, C., 2009. Both NR2A and NR2B subunits of the NMDA receptor are critical for long-term potentiation and long-term depression in the lateral amygdala of horizontal slices of adult mice. *Learn Mem* 16, 395-405.

Norrholm, S.D., Ouimet, C.C., 2001. Altered dendritic spine density in animal models of depression and in response to antidepressant treatment. *Synapse* 42, 151-163.

Notter, T., Meyer, U., 2017. Microglia and schizophrenia: where next? *Mol Psychiatry* 22, 788-789.

O'Connor, J.J., Coogan, A.N., 1999. Actions of the pro-inflammatory cytokine IL-1  $\beta$  on central synaptic transmission. *Exp Physiol* 84, 601-614.

Palucha, A., Branski, P., Szewczyk, B., Wieronska, J.M., Klak, K., Pilc, A., 2005. Potential antidepressant-like effect of MTEP, a potent and highly selective mGluR5 antagonist. *Pharmacol Biochem Behav* 81, 901-906.

Paolicelli, R.C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., Giustetto, M., Ferreira, T.A., Guiducci, E., Dumas, L., Ragozzino, D., Gross, C.T., 2011. Synaptic pruning by microglia is necessary for normal brain development. *Science* 333, 1456-1458.

Parkhurst, C.N., Yang, G., Ninan, I., Savas, J. N., Yates, J. R., Lafaille, J. J., ... Gan, W.-B., 2013. Microglia promote learning-dependent synapse formation through BDNF. *Cell*, Cell, pp. 1596–1609.

Pascual, O., Ben Achour, S., Rostaing, P., Triller, A., Bessis, A., 2012. Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission, *Proc Natl Acad Sci U S A*, pp. E197-205.

Pechlivanova, D.M., Tchekalarova, J.D., Alova, L.H., Petkov, V.V., Nikolov, R.P., Yakimova, K.S., 2012. Effect of long-term caffeine administration on depressive-like behavior in rats exposed to chronic unpredictable stress. *Behav Pharmacol* 23, 339-347.

Petersen, C.C., Malenka, R.C., Nicoll, R.A., Hopfield, J.J., 1998. All-or-none potentiation at CA3-CA1 synapses. *Proc Natl Acad Sci U S A* 95, 4732-4737.

Piccinin, S., Di Angelantonio, S., Piccioni, A., Volpini, R., Cristalli, G., Fredholm, B.B., Limatola, C., Eusebi, F., Ragozzino, D., 2010. CX3CL1-induced modulation at CA1 synapses reveals multiple mechanisms of EPSC modulation involving adenosine receptor subtypes. *J Neuroimmunol* 224, 85-92.

Queiroz, G., Gebicke-Haerter, P.J., Schobert, A., Starke, K., von Kugelgen, I., 1997. Release of ATP from cultured rat astrocytes elicited by glutamate receptor activation. *Neuroscience* 78, 1203-1208.

Ragozzino, D., Di Angelantonio, S., Trettel, F., Bertollini, C., Maggi, L., Gross, C., Charo, I.F., Limatola, C., Eusebi, F., 2006. Chemokine fractalkine/CX3CL1 negatively modulates active glutamatergic synapses in rat hippocampal neurons. *J Neurosci* 26, 10488-10498.

Ransohoff, R.M., 2016. A polarizing question: do M1 and M2 microglia exist? *Nat Neurosci* 19, 987-991.

Rex, C.S., Lin, C.Y., Kramar, E.A., Chen, L.Y., Gall, C.M., Lynch, G., 2007. Brain-derived neurotrophic factor promotes long-term potentiation-related cytoskeletal changes in adult hippocampus. *J Neurosci* 27, 3017-3029.

Riazi, K., Galic, M.A., Kentner, A.C., Reid, A.Y., Sharkey, K.A., Pittman, Q.J., 2015. Microglia-dependent alteration of glutamatergic synaptic transmission and plasticity in the hippocampus during peripheral inflammation. *J Neurosci* 35, 4942-4952.

Rimmerman, N., Schottlender, N., Reshef, R., Dan-Goor, N., Yirmiya, R., 2017. The hippocampal transcriptomic signature of stress resilience in mice with microglial fractalkine receptor (CX3CR1) deficiency. *Brain Behav Immun* 61, 184-196.

Rogers, J.T., Morganti, J.M., Bachstetter, A.D., Hudson, C.E., Peters, M.M., Grimmig, B.A., Weeber, E.J., Bickford, P.C., Gemma, C., 2011. CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. *J Neurosci* 31, 16241-16250.

Sahraian, A., Ghanizadeh, A., Kazemeini, F., 2015. Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior, a randomized placebo-controlled clinical trial, *Trials*.

Schafer, D.P., Lehrman, E.K., Stevens, B., 2013. The "Quad-partite" Synapse: Microglia-Synapse Interactions in the Developing and Mature CNS. *Glia* 61, 24-36.

Schiavone, S., Jaquet, V., Trabace, L., Krause, K.H., 2013. Severe Life Stress and Oxidative Stress in the Brain: From Animal Models to Human Pathology, *Antioxid Redox Signal*, pp. 1475-1490.

Schneider, H., Pitossi, F., Balschun, D., Wagner, A., del Rey, A., Besedovsky, H.O., 1998. A neuromodulatory role of interleukin-1beta in the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America* 95, 7778-7783.

Seo, J.S., Park, J.Y., Choi, J., Kim, T.K., Shin, J.H., Lee, J.K., Han, P.L., 2012. NADPH oxidase mediates depressive behavior induced by chronic stress in mice. *J Neurosci* 32, 9690-9699.

Setiawan, E., Wilson, A.A., Mizrahi, R., Rusjan, P.M., Miler, L., Rajkowska, G., Suridjan, I., Kennedy, J.L., Rekkas, P.V., Houle, S., Meyer, J.H., 2015. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry* 72, 268-275.

Song, M., Martinowich, K., Lee, F.S., 2017. BDNF at the synapse: why location matters. *Molecular Psychiatry*, 1370-1375.

Su, K.P., Huang, S.Y., Peng, C.Y., Lai, H.C., Huang, C.L., Chen, Y.C., Aitchison, K.J., Pariante, C.M., 2010. Phospholipase A2 and cyclooxygenase 2 genes influence the risk of interferon-alpha-induced depression by regulating polyunsaturated fatty acids levels. *Biological psychiatry* 67, 550-557.

Su, K.P., Lai, H.C., Yang, H.T., Su, W.P., Peng, C.Y., Chang, J.P., Chang, H.C., Pariante, C.M., 2014. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. *Biological psychiatry* 76, 559-566.

Svenningsson, P., Bateup, H., Qi, H., Takamiya, K., Huganir, R.L., Spedding, M., Roth, B.L., McEwen, B.S., Greengard, P., 2007. Involvement of AMPA receptor phosphorylation in antidepressant actions with special reference to tianeptine. *Eur J Neurosci* 26, 3509-3517.

Tynan, R.J., Weidenhofer, J., Hinwood, M., Cairns, M.J., Day, T.A., Walker, F.R., 2012. A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. *Brain, behavior, and immunity* 26, 469-479.

Vilhardt, F., Haslund-Vinding, J., Jaquet, V., McBean, G., 2017. Microglia antioxidant systems and redox signalling. *Br J Pharmacol* 174, 1719-1732.

Vivash, L., O'Brien, T.J., 2016. Imaging Microglial Activation with TSPO PET: Lighting Up Neurologic Diseases? *J Nucl Med* 57, 165-168.

Wang, L., Shen, X., Wu, Y., Zhang, D., 2016. Coffee and caffeine consumption and depression: A meta-analysis of observational studies. *Aust N Z J Psychiatry* 50, 228-242.

Yirmiya, R., Goshen, I., 2011. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain, behavior, and immunity* 25, 181-213.

Yirmiya, R., Rimmerman, N., Reshef, R., 2015. Depression as a microglial disease. *Trends Neurosci* 38, 637-658.

Yoshida, T., Ishikawa, M., Niitsu, T., Nakazato, M., Watanabe, H., Shiraishi, T., Shiina, A., Hashimoto, T., Kanahara, N., Hasegawa, T., Enohara, M., Kimura, A., Iyo, M., Hashimoto, K., 2012. Decreased serum levels of mature brain-derived neurotrophic factor (BDNF), but not its precursor proBDNF, in patients with major depressive disorder. *PLoS One* 7, e42676.

Yue, N., Huang, H., Zhu, X., Han, Q., Wang, Y., Li, B., Liu, Q., Wu, G., Zhang, Y., Yu, J., 2017. Activation of P2X7 receptor and NLRP3 inflammasome assembly in hippocampal glial cells mediates chronic stress-induced depressive-like behaviors. *J Neuroinflammation*.

Zhang, J., Malik, A., Choi, H.B., Ko, R.W., Dissing-Olesen, L., MacVicar, B.A., 2014a. Microglial CR3 activation triggers long-term synaptic depression in the hippocampus via NADPH oxidase. *Neuron* 82, 195-207.

Zhang, J., Yao, W., Hashimoto, K., 2016. Brain-derived Neurotrophic Factor (BDNF)-TrkB Signaling in Inflammation-related Depression and Potential Therapeutic Targets, *Curr Neuropharmacol*, pp. 721-731.

Zhang, J.C., Wu, J., Fujita, Y., Yao, W., Ren, Q., Yang, C., Li, S.X., Shirayama, Y., Hashimoto, K., 2014b. Antidepressant effects of TrkB ligands on depression-like behavior and dendritic changes in mice after inflammation. *Int J Neuropsychopharmacol* 18, 77-83.

Zhang, X., Zhang, Z., Sha, W., Xie, C., Xi, G., Zhou, H., Zhang, Y., 2009. Electroconvulsive therapy increases glial cell-line derived neurotrophic factor (GDNF) serum levels in patients with drug-resistant depression. *Psychiatry Res* 170, 273-275.

Zheng, L.S., Kaneko, N., Sawamoto, K., 2015. Minocycline treatment ameliorates interferon-alpha-induced neurogenic defects and depression-like behaviors in mice. *Frontiers in cellular neuroscience* 9, 5.

Zunszain, P.A., Anacker, C., Cattaneo, A., Choudhury, S., Musaelyan, K., Myint, A.M., Thuret, S., Price, J., Pariante, C.M., 2012. Interleukin-1beta: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 37, 939-949.